

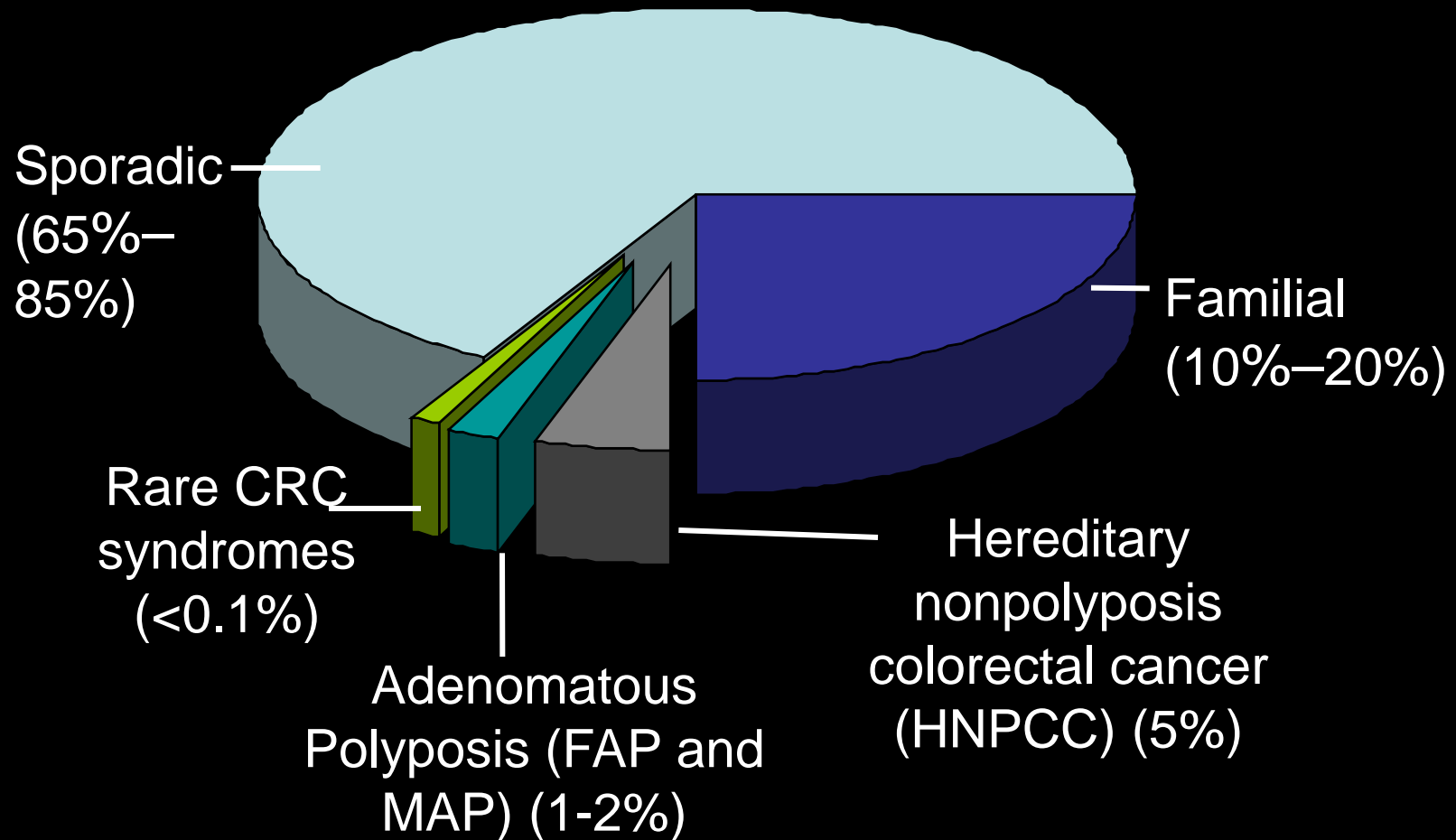
Clinical Aspects, Screening and Surveillance in Lynch Syndrome

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Hereditary Syndromes in GI Cancer

- Hereditary Colorectal Cancer
 - Adenomatous Polyposis (FAP and MAP)
 - Lynch Syndrome (Hereditary Nonpolyposis Colorectal Cancer -HNPCC)
 - Hamartomatous Polyposis Syndromes
 - Hereditary Colorectal Cancer X
- Hereditary Pancreatic Cancer
- Hereditary Gastric Cancer
- GI cancers associated with other hereditary syndromes

Causes of Hereditary Susceptibility to CRC



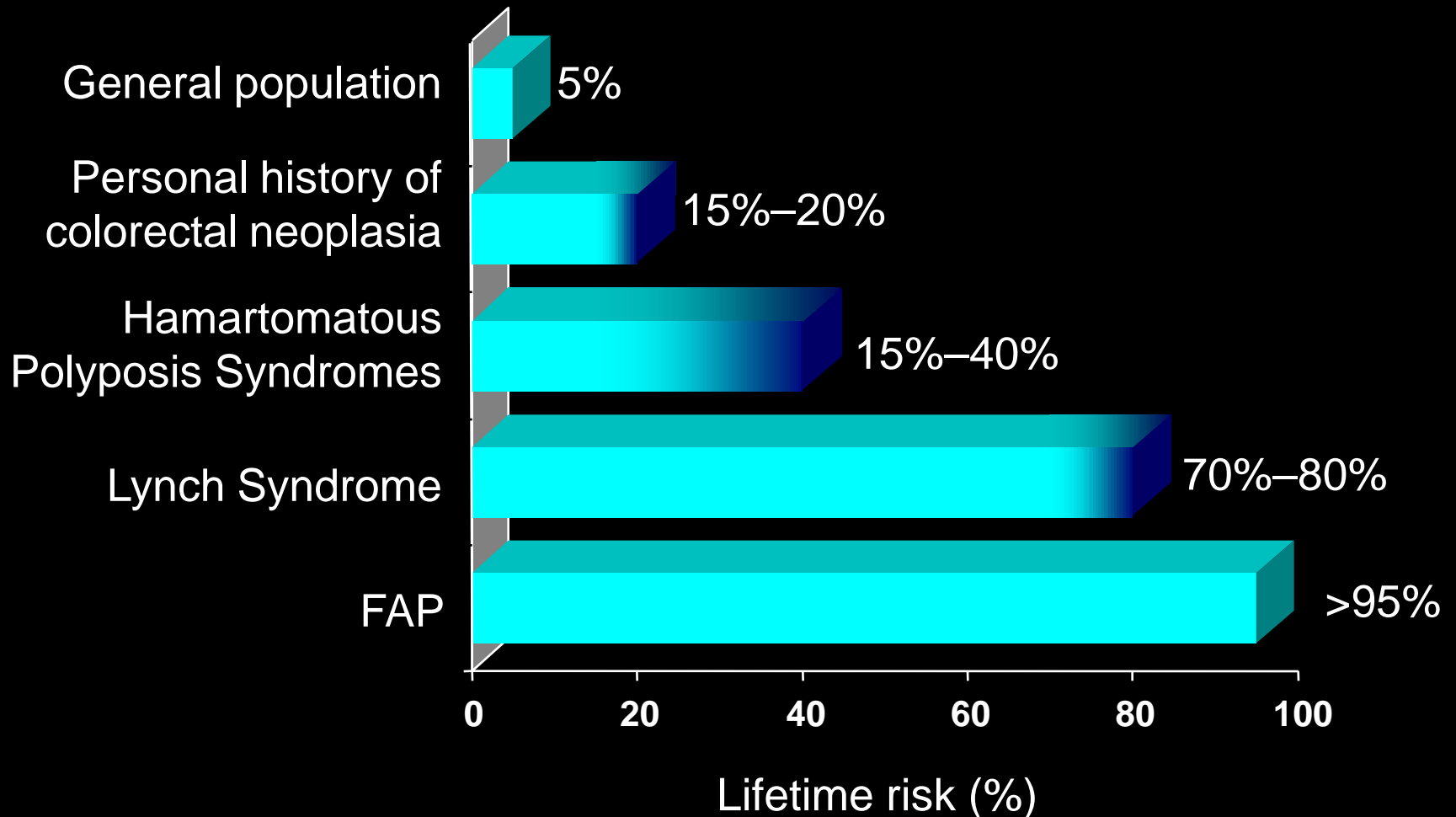
Two main challenges to consider...

- How do we find the patients?
- Once we find them, how do we manage them?

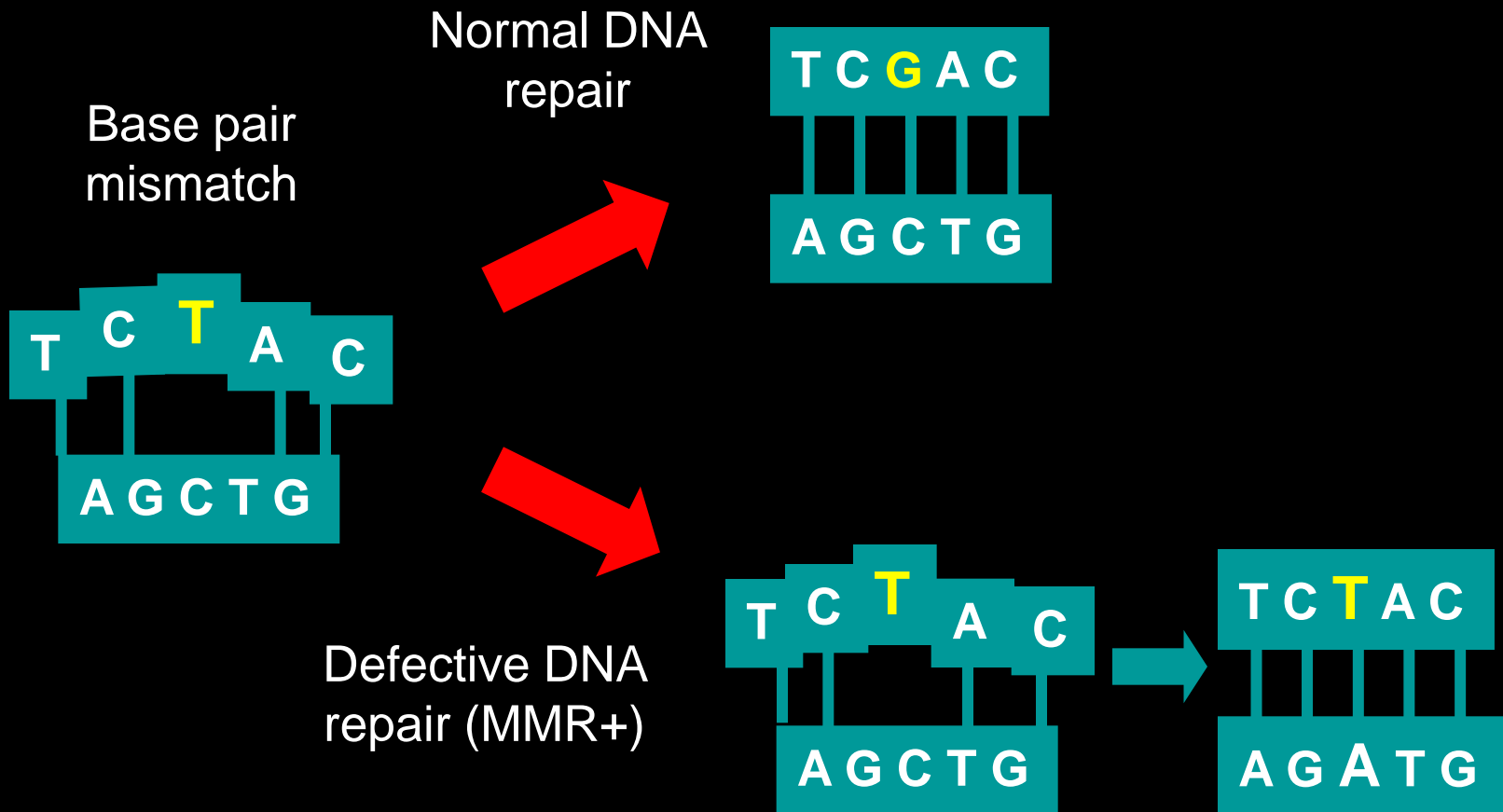
How is management of hereditary cancers different than sporadic cancers?

- Surgical management of cancer/polyps
- Screening and surveillance post treatment of primary cancer
- Surveillance for associated cancers
- Screening and surveillance of family members
- Reproductive counseling

Risk of Colorectal Cancer (CRC)

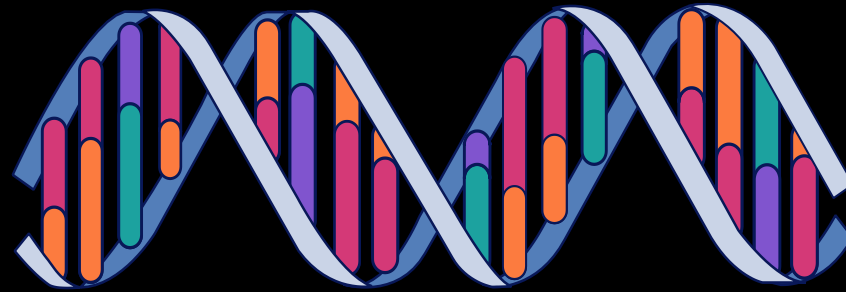


HNPPC Results From Failure of Mismatch Repair (MMR) Genes



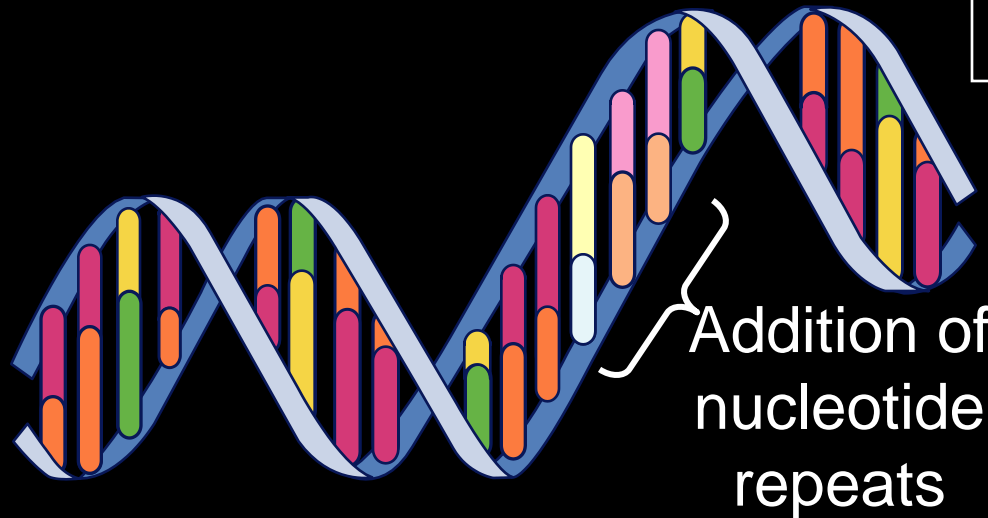
Mismatch Repair Failure Leads to Microsatellite Instability (MSI)

Normal

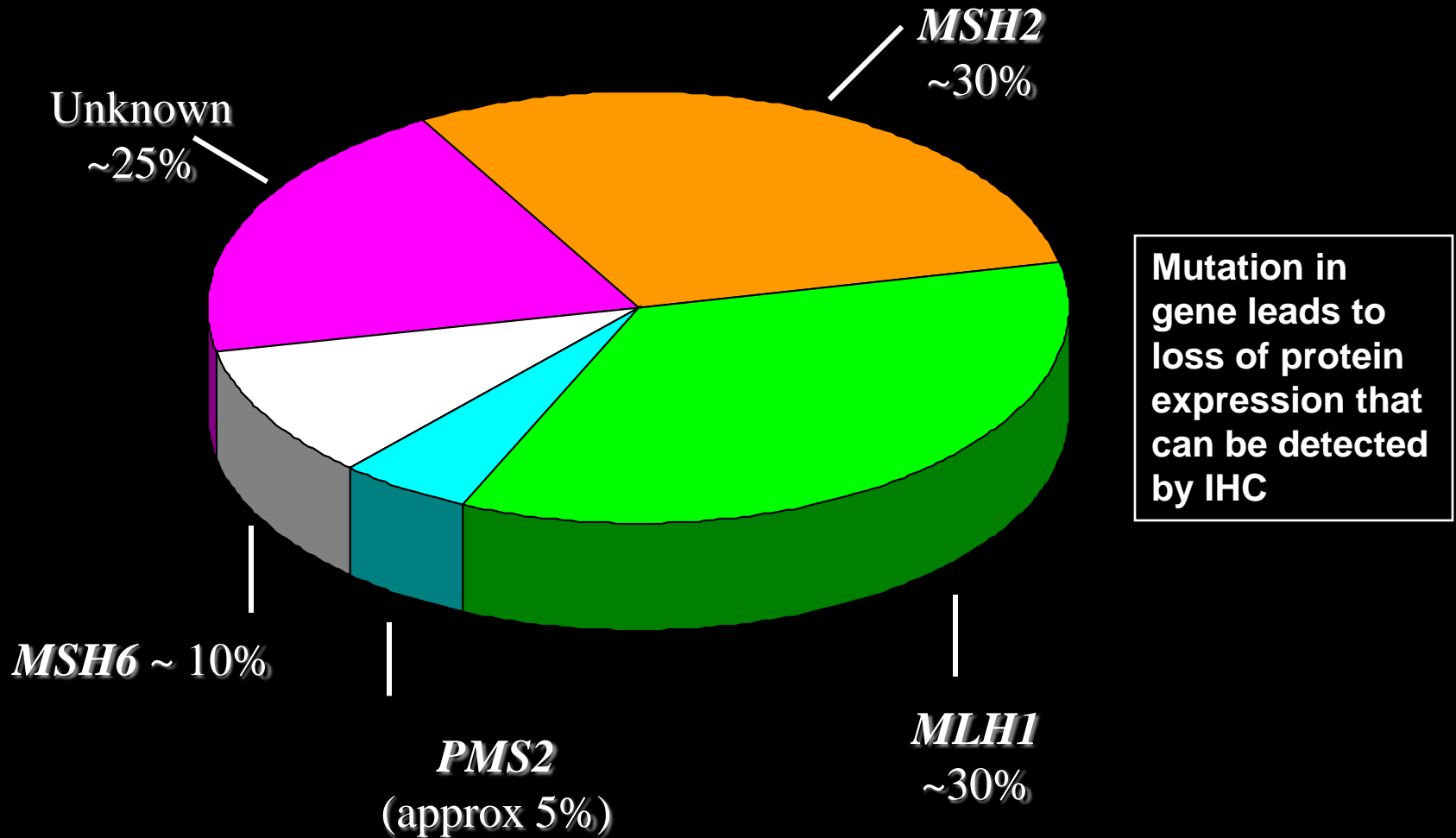


Approximately
15% of CRCs
have evidence of
MSI

Microsatellite
instability



Contribution of Gene Mutations to HNPCC Families



Approximately 15% of ALL colorectal cancers have evidence of microsatellite instability

- Most MSI-high tumors are NOT caused by inherited mismatch repair gene mutations
 - due to somatic hypermethylation of MLH1 promoter
 - associated with BRAF mutations
- A subset of MSI high tumors have germline mismatch repair gene mutations
 - have to do genetic testing (peripheral blood DNA) to find these patients who have Lynch Syndrome

Lynch Syndrome – How do we find the patients?

Lots of options – too many options!

- Tumor testing
 - MSI
 - IHC
 - MSI and IHC
- Personal and family history
 - Amsterdam, Bethesda, and Jerusalem Guidelines
 - Prediction models
 - PREMM
 - MMR Predict
 - MMRPro

Is there a role for routine testing for MMR deficiency?

- Recommendations in literature for routine IHC and/or MSI testing for all CRCs
- Potential drawbacks
 - Cost and complexity of tumor testing
 - Genetic information without patient consent
 - High rate of sporadic MSI and loss of MLH1, particularly for older patients
 - Many patients requiring further genetic evaluation - high downstream costs
 - May still miss some
- Potential benefits
 - Most efficient way to find majority of CRC patients with Lynch Syndrome
 - May have therapeutic implications

Revised Bethesda Guidelines

- Colorectal cancer under age 50
- Synchronous or metachronous colorectal or HNPCC-associated tumor
- CRC with one or more FDR with CRC or other HNPCC tumor, one less than 50
- CRC with two or more relatives with CRC or other HNPCC tumor regardless of age

Jerusalem Recommendations

- Group of interested investigators met, debated, and made clinical recommendations about Lynch Syndrome
- Recommended that all CRCs in patients <70 years old be screened for LS either by IHC or MSI testing
 - this would detect all but ~14% of LS cases
 - IHC would also help determine which gene to test for
- Refer for genetic testing; greatest benefit comes to asymptomatic 1st and 2nd degree relatives
- Targeted cancer screening
- Precision/personalized treatment

Prediction Models for the Identification of Lynch Syndrome

RECENT MODELS

- MMRpredict
- MMRpro
- PREMM_{1,2}
- PREMM_{1,2,6}

Development of models based on proband and family history phenotypes +/- tumor testing

Barnetson et al. *N Engl J Med* 2006; 354: 2751-63

Chen et al. *JAMA* 2006; 296:1479-87

Balmana et al. *JAMA* 2006; 296:1469-78

Kastrinos et al. *Gastroenterology* 2011; 140:73-81

Prediction of MLH1/MSH2/MSH6 Mutations (PREMM_{1,2,6}) Model

1. Proband history

- Presence of colon cancer, other HNPCC cancer and/or adenomas
- Age of onset

2. Family history

- Presence of colon or other HNPCC cancer
- Youngest age at diagnosis



www.dfci.org/premm

Google “premm”

Predicted probability of mutation
in *MLH1/MSH2/MSH6*

Figure 1. PREMM_{1,2} Model as Presented on the Web

Proband Information

("Proband" refers to the individual being evaluated. Ideally, this individual should have a cancer or adenoma diagnosis.)

How many separate colorectal cancers has the proband had? None ☐ One ☐ Two or more ☐

If one, what was the age at diagnosis? *(if unknown, estimate)*

If two or more, what was the youngest age at diagnosis? *(if unknown, estimate)*

Has the proband had colonic adenoma(s)? Yes ☐ No ☐

What was the youngest age at diagnosis? *(if unknown, estimate)*

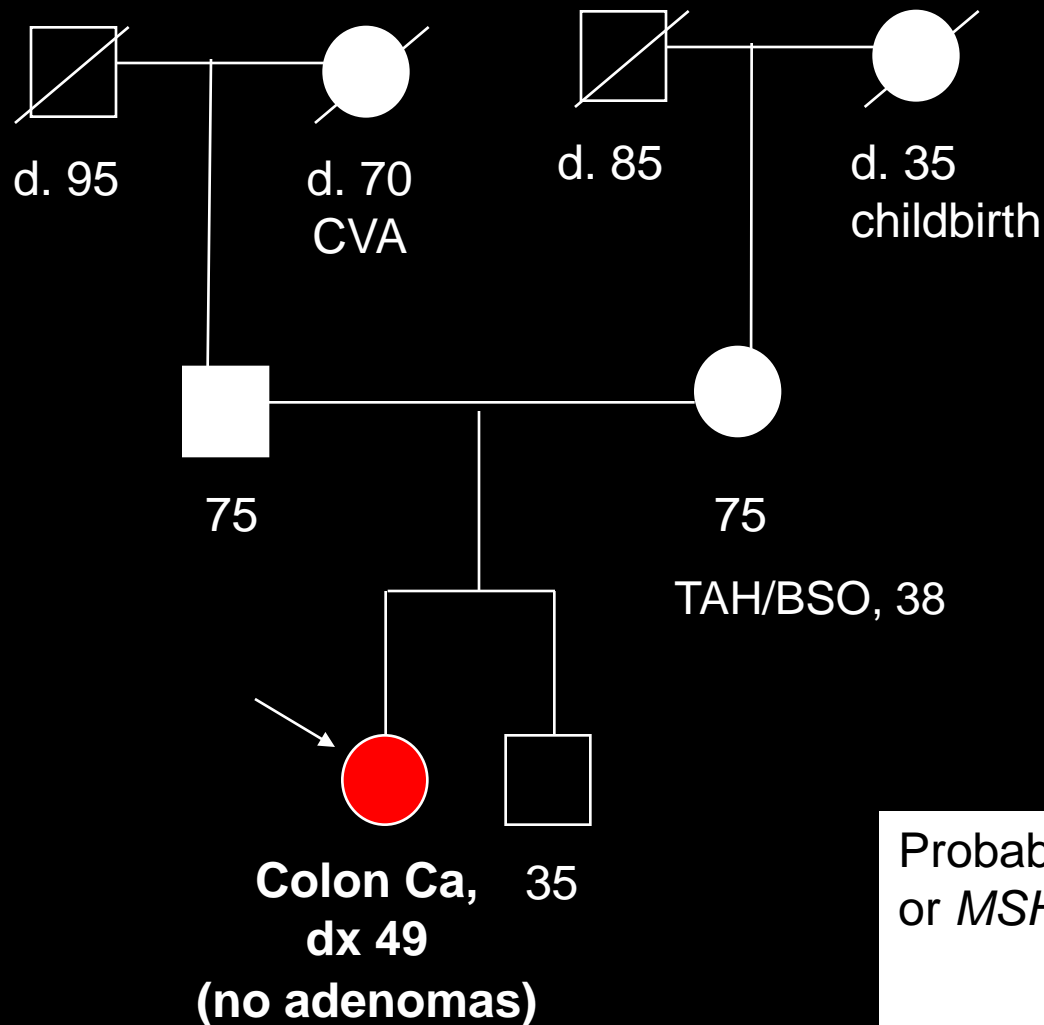
Has the proband had endometrial cancer? Yes ☐ No ☐

What was the youngest age at diagnosis? *(if unknown, estimate)*

Has the proband had another HNPCC-associated cancer? Yes ☐ No ☐

(Other HNPCC-associated cancers include ovary, stomach, small intestine, urinary tract/kidney, bile ducts, glioblastoma multiforme, sebaceous gland tumors, and pancreas.)

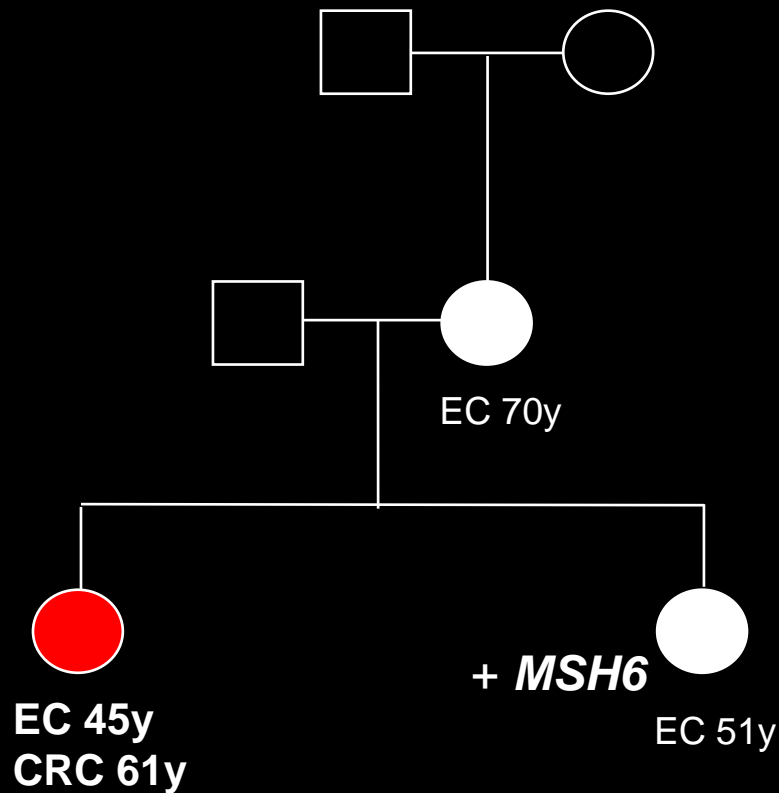
Isolated Early-Onset Colorectal Cancer



Probability of an *MLH1*
or *MSH2* in proband:

6%

PREMM_{1,2,6} Estimates



PREMM_{1,2,6} Estimates:

Any MMR mutation	47.3%
<i>MLH1</i> mutation	7.6%
<i>MSH2</i> mutation	15.1%
<i>MSH6</i> mutation	24.6%

Lynch Syndrome – Who Should be Referred?

IF tumor sample available:

- IHC and /or MSI testing -Advocate for set up of IHC for the four genes (MSH2, MLH1, PMS2 and MSH6) in each local pathology lab

IF tumor sample not available:

- Run PREMM model – if score >5% -REFER

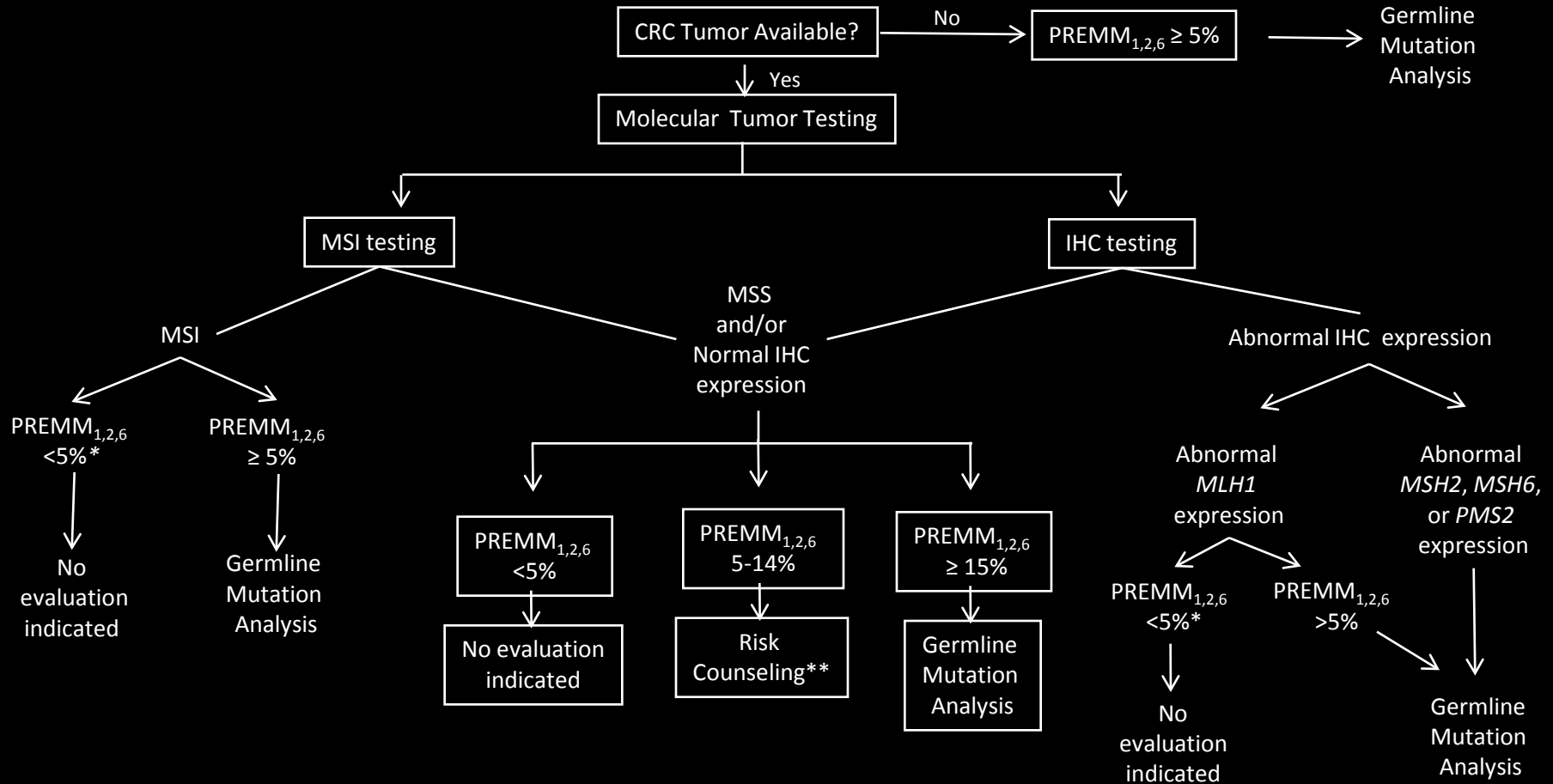
Family History Assessment by Oncologists

- 433 patients at first visit for treatment of CRC
- Physician documentation and patient self-reports compared
- Family history accurately obtained in 64% of patients
- Total numbers of family cancers inversely related to accuracy (OR 0.5, $p < 0.001$)

Family History Assessment in Clinical Practice

- Often not comprehensive
- Frequently limited to first-degree relatives because of time constraints or unreliable information
- Restricted to include only certain cancer types
 - e.g. “Any history of colon cancer in your family?”
- Relationship between different cancers (e.g. colon and endometrial CA) may be missed

Evaluation for Genetic Predisposition in Patients with Non-polyposis Colorectal Cancer



CRC=colorectal cancer; MSI=microsatellite instability; MSS=microsatellite stable; IHC=immunohistochemistry

Consider *BRAF* or *MLH1* hypermethylation testing;** *Surveillance recommendations based on personal and family history**

Caveats/Limitations

- No test (IHC, MSI, or models) is perfect – clinical judgment supersedes if the answer surprises you
- Limited data on performance in non-Caucasian ethnicities
- MSH6 and PMS2 IHC may be particularly unreliable

Genetic Malpractice

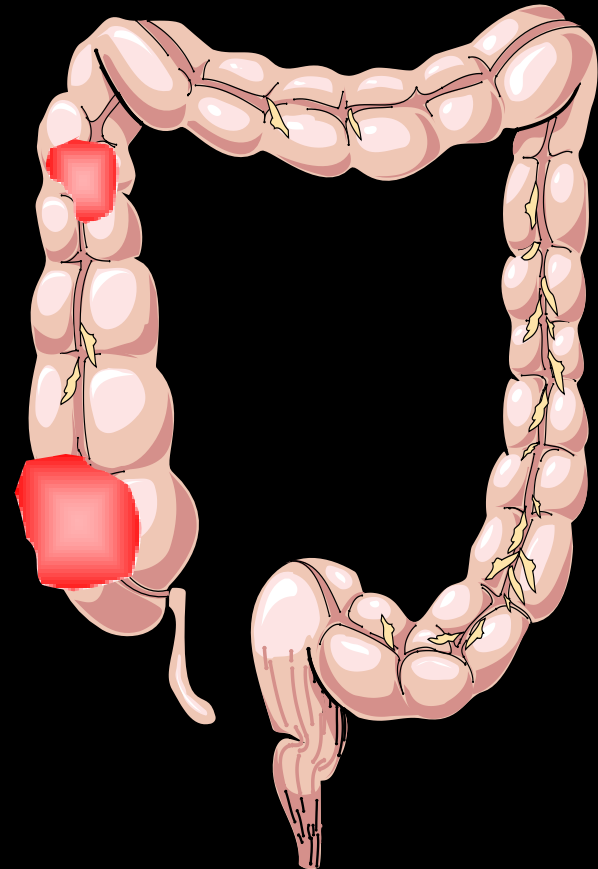
- Failure to make diagnosis and use proper diagnostic tools (family history and/or genetic testing)
- Failure to recommend adequately aggressive cancer surveillance
- Failure to recommend surveillance or prophylactic surgery for associated cancers
- Failure of “duty to warn” family members

Coming down the pipeline?

- Errors in interpreting test results
- Drug toxicity due to lack of use of pharmacogenomic tests

Clinical Features of HNPCC (Lynch Syndrome)

- Early but variable age at CRC diagnosis (~45 years)
- Multiple primary cancers
- Tumor site in proximal colon predominates
- Extracolonic cancers: endometrium, ovary, stomach, urinary tract, small bowel, bile ducts, sebaceous skin tumors



Muir-Torre Syndrome (MTS)

- Lynch Syndrome
 - usually, but not always MSH2
- Plus, skin neoplasms:
 - sebaceous neoplasms (adenomas, carcinomas)
 - keratoacanthomas
 - other (BCC, SCC, melanoma)

Estimating Cancer Risk in Hereditary GI Cancer Syndromes

- Historically, most cancer risks are estimated from families with a strong family history of early-onset cancers
- Issues:
 - Overestimation of age-specific cumulative risk
 - Incomplete testing of full pedigree
 - Analyses based on observed genotype lack power

Redefining Cancer Risk in Hereditary GI Cancer Syndromes

- Recent reports employ new analytical tools

Modified Segregation Analysis

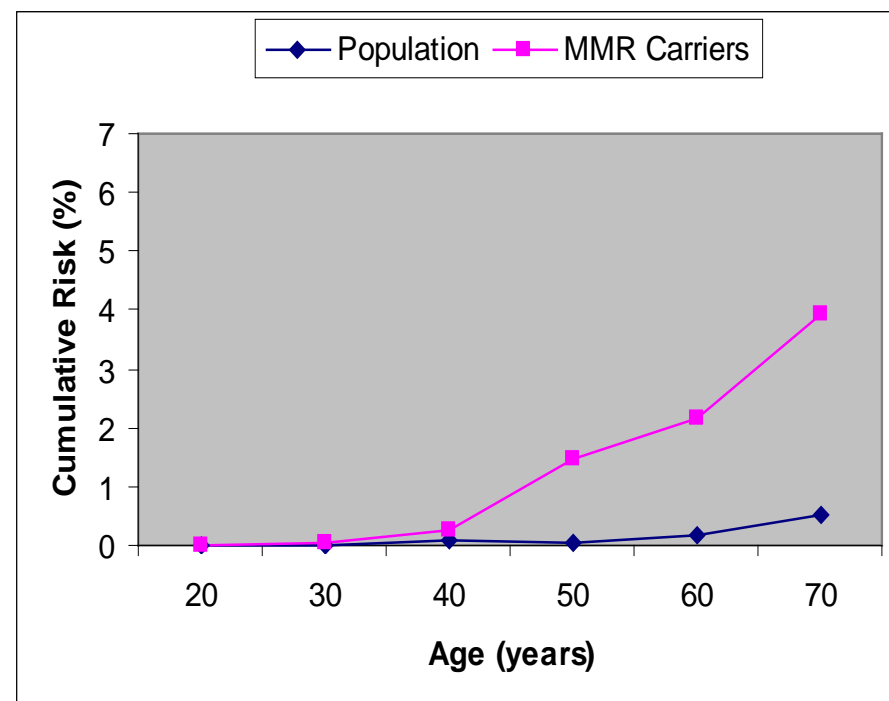
- Corrects for ascertainment and overestimation of penetrance
- Accounts for genotyped and ungenotyped relatives
- Likelihood for each pedigree conditioned on the phenotype of the pedigree, the probands' age of diagnosis and gene mutation carrier status

Original Contribution. JAMA. 2009;302(16):1790-1795

Risk of Pancreatic Cancer in Families With Lynch Syndrome

Fay Kastrinos, MD, MPH; Bhramar Mukherjee, PhD; Nabihah Tayob, MS; Fei Wang, MS; Jennifer Sparr, MD; Victoria M. Raymond, MS; Prathap Bandipalliam, MD; Elena M. Stoffel, MD, MPH; Stephen B. Gruber, MD, MPH, PhD; Sapna Syngal, MD, MPH

Age*	Cumulative Risk Population† %	Cumulative Risk MMR Carriers % (95% CI)
20	0	0
30	0.00	0.04
40	0.01	0.26
50	0.04	1.46 (0.56, 3.22)
60	0.18	2.16
70	0.52	3.95 (1.52, 6.63)



†Surveillance Epidemiology and End Results 2001-2005

Colorectal and Other Cancer Risks for Carriers and Noncarriers From Families With a DNA Mismatch Repair Gene Mutation: A Prospective Cohort Study

Aung Ko Win, Joanne P. Young, Noralane M. Lindor, Katherine M. Tucker, Dennis J. Ahnen, Graeme P. Young, Daniel D. Buchanan, Mark Clendenning, Graham G. Giles, Ingrid Winship, Finlay A. Macrae, Jack Goldblatt, Melissa C. Southey, Julie Arnold, Stephen N. Thibodeau, Shanaka R. Gunawardena, Bharati Bapat, John A. Baron, Graham Casey, Steven Gallinger, Loïc Le Marchand, Polly A. Newcomb, Robert W. Haile, John L. Hopper and Mark A. Jenkins

- 446 unaffected MMR gene mutation carriers + 1,029 unaffected relatives without gene mutations in CCFR
- Subjects followed every 5 years
 - prospective design minimizes ascertainment bias: observation time for carriers and noncarriers commenced before cancer diagnosis

Other Cancer Risks for Carriers and Noncarriers From Families With Lynch Syndrome

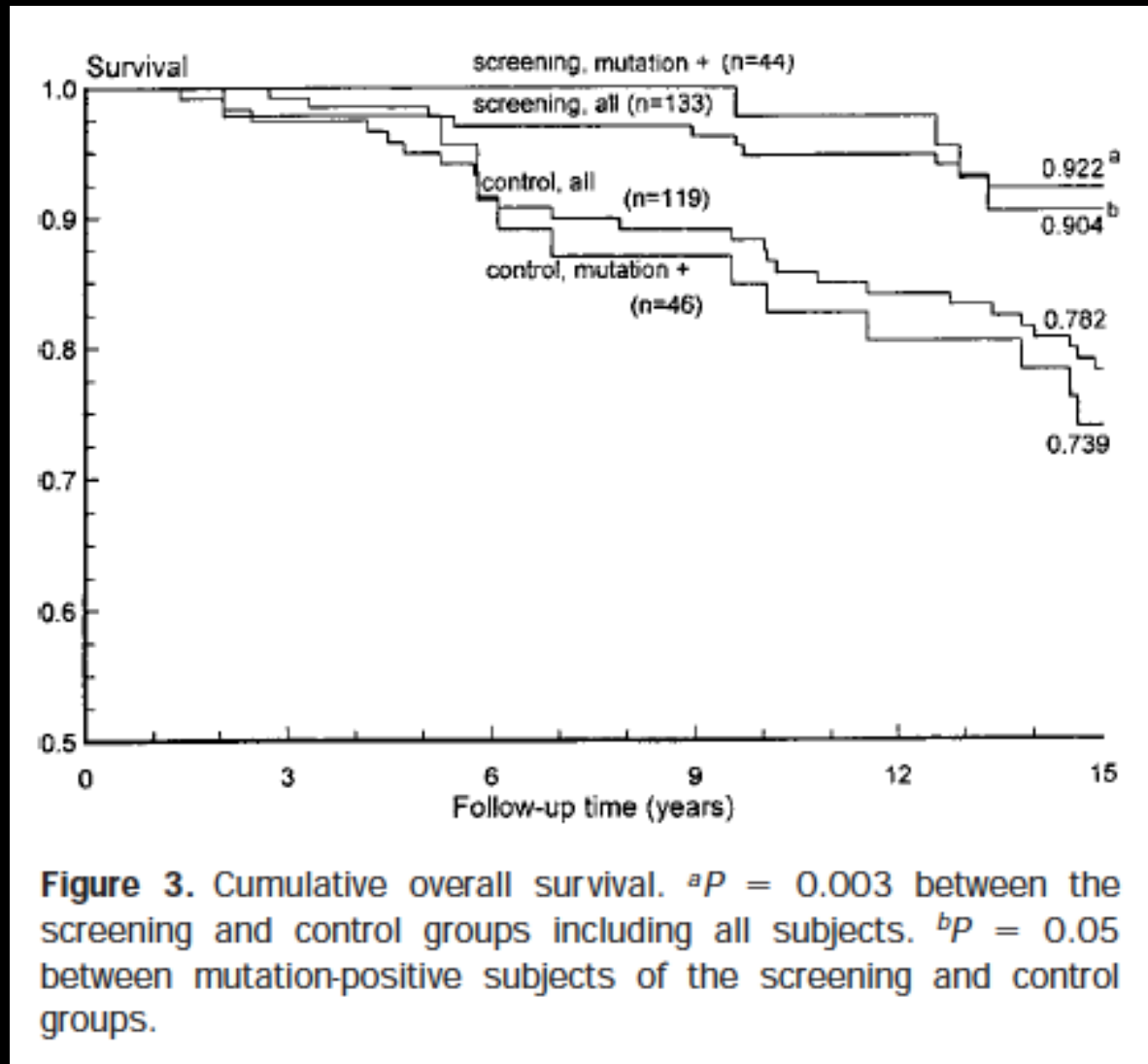
Cancer	Observed No.	Expected No.	SIR*	95% CI	P
Carriers					
Colorectal cancer	16	0.78	20.48	11.71 to 33.27	<.001
Endometrial cancer	6	0.20	30.62	11.24 to 66.64	<.001
Ovary cancer	3	0.16	18.81	3.88 to 54.95	<.001
Renal cancer	3	0.27	11.22	2.31 to 32.79	<.001
Pancreas cancer	2	0.19	10.68	2.68 to 47.70	.001
Gastric cancer	2	0.20	9.78	1.18 to 35.30	.009
Urinary bladder cancer	2	0.21	9.51	1.15 to 34.37	.009
Breast cancer	7	1.77	3.95	1.59 to 8.13	.001
Prostate cancer	3	1.21	2.49	0.51 to 7.27	.18
Noncarriers					
Colorectal cancer	5	4.88	1.02	0.33 to 2.39	.97
Lung cancer	3	4.68	0.64	0.13 to 1.87	.51
Breast cancer	5	6.95	0.72	0.23 to 1.68	.52
Prostate cancer	9	5.53	1.63	0.74 to 3.09	.18

*Age-, Sex-, and Country-Specific SIRs for Carriers & Noncarriers Compared With the General Population

Surveillance Recommendations for HNPCC Patients

Malignancy	Intervention	Recommendation
Colorectal cancer	Colonoscopy	Begin at age 20–25, repeat every 1–2 years
Endometrial cancer	◆ Transvaginal ultrasound ◆ Endometrial aspirate	Annually, starting at age 30–35

Surveillance Reduces Mortality



Surveillance for Urological Cancers in Lynch Syndrome

Urinary cytology does not work in this setting

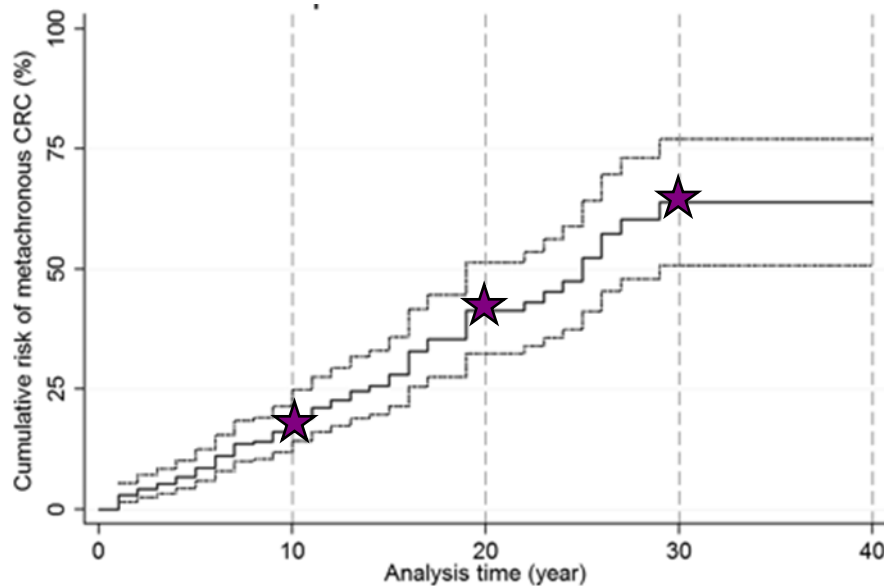
- urinary cytology missed most patients with urological cancers
 - Danish HNPCC Registry, 977 people had 1,868 screening tests
 - 2 (0.1%) had true positive tests that detected cancer
 - 22 (1%) had false positive tests
 - 14 (1.4%) developed urological tract tumors during study (5 after neg. test)
- Always work up of blood in the urine
 - Annual urinalysis

Prophylactic Surgery Options for HNPCC-Associated Mutation Carriers

- Colon cancer options include subtotal colectomy vs total colectomy (esp. important at time of CRC diagnosis!)
- Uterine and ovarian cancer options include hysterectomy and oophorectomy – prophylactic TAH/BSO completely prevents gynecologic tumors
- Individual patient decision dependent on compliance with screening, efficacy of screening tests, need for surgical resection

Metachronous colorectal cancer risk for mismatch repair gene mutation carriers: the advantage of more extensive colon surgery

Susan Parry, Aung Ko Win., Bryan Parry, Finlay A Macrae, Lyle C Gurrin, James M Church, John A Baron, Graham G Giles, Barbara A Leggett, Ingrid Winship, Lara Lipton, Graeme P Young, Joanne P Young, Caroline J Lodge, Melissa C Southey, Polly A Newcomb, Loïc Le Marchand, Robert W Haile, Noralane M Lindor, Steven Gallinger, John L Hopper, Mark A Jenkins



- 382 gene mutation carriers with CRC
- 50 subjects had extensive colectomy: 0% metachronous CRC
- 332 subjects had segmental resections: 74 (22%) had metachronous CRC (incidence rate 23.6; 95% CI 18.8-29.7 per 1000 p-yrs)
- Risk of metachronous CRC reduced by 31% (95% CI 12% to 46%; $p=0.002$) for every 10 cm of bowel removed

- Metachronous CRC risk impacts informed decision-making about the extent of primary surgical resection

Aspirin and Lynch Syndrome

- Clinical Trial initiated to determine impact of ASA and “resistant starch” over 4 years on recurrent colorectal adenomas in LS (CAPP2)
 - Randomized 861 LS patients to daily 600 mg/day ASA vs placebo (matrix design with resistant starch)
 - RR for recurrent adenomas was 1.0 (mean 29 months)
 - Average age ~45; no excess toxicity from the ASA
 - Trial terminated, patients followed for another 4 years

Aspirin and Lynch Syndrome

- Patients followed for another 4 years (off study drugs)
 - mean follow-up 55.7 months
- Hazard Ratio for CRC among ASA takers = 0.63
- Hazard ratio for CRC was 0.41 (0.19-0.86), if they took ASA >2 years and followed for 11 years
- Significant reduction in endometrial cancer (not reported in this study)
- No prevention of adenomatous polyps; significant reduction in cancer

Our approach to the Lynch Syndrome Mutation Carrier...for all patients

- Colonoscopic surveillance every year – careful exam, do not routinely use chromoendoscopy etc.
- Subtotal colectomy if CRC develops
- Transvaginal ultrasound and endometrial biopsy starting at 35 for women
- Strongly consider prophylactic TAH/BSO in perimenopausal years
- Annual skin exam
- EGD every 3 years

Our approach to the Lynch Syndrome Mutation Carrier... on case by case basis

- Pancreatic cancer surveillance (EUS/MRI) if mutation carrier in family with pancreatic cancer
- Urine cytology if mutation carrier in family with GU cancer
- Capsule endoscopy if mutation carrier in family with small bowel cancer
- Aspirin after consideration of risk/benefits (most patients have decided against it thus far due to dose)

What we don't do now, but may in the future...

- Tailor surveillance to gene mutated
 - ? Delay surveillance for *MSH6* and/or *PMS2* carriers
 - ? More extracolonic surveillance for *MSH2* carriers

Thank you!

Questions?

Comments?